THE NIH GENES AND ENVIRONMENT INITIATIVE (GEI)
PROPOSED FOUR-YEAR PLAN, 8/18/06 Draft

Overview

The Genes and Environment Initiative (GEI) is a four-year, NIH-wide program proposed in the President's FY2007 budget and currently awaiting Congressional approval. If approved by Congress, $40M per year in FY2007 through FY2010 will be devoted to GEI. Of this total, $26M will be allocated to the Genetics Program to identify major genetic susceptibility factors for diseases of substantial public health impact, and $14M per year will be allocated to the Exposure Biology Program to develop new technology for more precise measurement of exposure and response to environmental toxins, dietary factors, physical activity, psychosocial stress, and addictive substances. In addition, NIEHS will commit up to $32M during FY07 to FY10 to the Exposure Biology Program, and NHGRI will commit up to $3.5M in sequencing costs. GEI is being developed and implemented by an NIH-wide Coordinating Committee, administratively led by NHGRI and NIEHS. Several ICs have agreed to lead specific GEI components, and will administer all applications received for these components in collaboration with GEI Coordinating Committee and Subcommittee members. As noted in the Table, GEI funding is treated as a set-aside for FY2007-FY2010 which reverts to the IC base in FY2011 and beyond.

The GEI Genetics Program will use genome-wide association (GWA) genotyping and other genomic research methodologies to identify the major susceptibility and etiologic factors for complex diseases of significant public health impact. This program will support: (1) initial GWA discovery studies; (2) development of data analytic methods; (3) replication and fine mapping studies; (4) targeted sequencing; (5) database development; and pilot efforts in (6) functional studies and (7) clinical translation.

The GEI Exposure Biology Program will develop the tools that are needed to understand how environmental toxins, diet, physical activity, psychosocial stress, and addictive substances contribute to the development of disease. This program will support: (1) development of environmental sensors for measurement of toxins, dietary intake, physical activity, psychosocial stress, and addictive substances; (2) development of markers of biological response via common pathogenic mechanisms such as oxidative stress, epigenetic modifications, and DNA damage; (3) integration of biological responses with the development of biosensors; and (4) application of novel assays and biomarkers to GWA studies of gene-environment interaction.

GENETICS PROGRAM

Rationale

Many large population studies have been supported by NIH to collect DNA samples and perform extensive phenotyping and exposure measures. These populations are now well suited for application of GWA genotyping, either as initial "discovery" studies interrogating the entire genome, or as follow-up "replication" studies to validate initial

results with additional population samples. A critical initial recommendation of the GEI Coordinating Committee is that GEI's Genetics Program not be limited solely to collection of GWA genotype data; six additional components, as described above, are thus proposed for inclusion in GEI. The proposed distribution of funds among these components has been agreed upon by the GEI Coordinating Committee (Attachment 2)

Genome Wide Association Studies

Three GEI-GWA RFAs will be released as soon as approval is received from the IC Directors. An initial nine studies will be solicited for genotyping through RFA HG-06-033, which will be re-issued in FY08 and FY09 to support an additional six studies. Genotyping Facilities and a Coordinating Center will be supported through HG-06-014 and HG-06-032. Ten percent of GEI Genetics funds, or $2.6M/yr, will be set aside for intramural investigators wishing to apply, and for support of the database at NCBI.

In addition to the $40M allocated for initial GWA genotyping, the Replication/Fine Mapping Working Group recommends allocating $7M to replication studies, to be solicited in the GWA RFAs. The Data Analysis Working Group also recommends allocating $7M for statistical analyses of the resulting GWA data through these RFAs.

Data Analysis

In addition to providing substantial analysis support to investigators funded through the GWA RFAs, the Data Analysis Working Group recommends adding $1.8M in analysis funds to the Sequencing component. They also propose three workshops and two RFAs:

- Annual workshops on analytic methods for GWA studies ($30K/yr) in FY08 - FY10
- RFA on development of statistical theory and methods for analysis of sequencing data ($2M/yr) in FY07 – FY09
- RFA on development of statistical theory and methods for analysis of gene-environment interactions ($2M/yr) in FY08-FY10

Replication/Fine Mapping

In addition to providing substantial support for replication studies to investigators funded through the GWA RFAs, the Replication/Fine Mapping Working Group anticipates an additional total of $5-7M to be committed to replication and fine mapping studies in the later years of GEI. This would likely involve a new competition.

Sequencing

Identification of new variants in genomic regions associated with diseases and traits will be critical to determining causative genes. The Sequencing Working Group recommends that NHGRI donate sufficient sequencing capacity to sequence candidate genes/regions identified through GWA studies. Roughly 12 projects will be supported to sequence 15 regions of 80kb each in 48 samples, or 1.2 Mb per project. In addition, a workshop on criteria for selection of regions to be sequenced is proposed for early FY07.

Database

The Database Working Group recommends allocating $1.25M per year in FY07 – FY10 in intramural funds to development and management of the GEI database. This will include GWA genotyping data, phenotype and environmental exposure data from the GWA studies, and replication/fine mapping data produced from these studies. SNPs identified in sequencing and functional studies will be deposited in dbSNP.

Functional Studies

The GEI Coordinating Committee recognizes that GEI cannot support the full range of functional studies likely to arise from initial GWA results, but proposes to support initial pilot efforts in this area, including two workshops, a supplement, and an RFA:

- Workshop on research directions in functional studies based on GWA findings in FY07
- Workshop on bioinformatics tools and resources to facilitate functional studies in FY08
- Supplement to the Knock-Out Mouse Project ($700K/yr) in FY08 – FY10
- RFA on functional analysis of genetic variants identified through GWA studies ($5M/yr) in FY09-FY10

Translation

Here again GEI must be limited to pilot efforts, including one workshop and two RFAs:

- Workshop on identifying barriers to bench-to-bedside translation in FY07
- RFA for pilot translational studies on known variants ($2.4M/yr) in FY08-FY09
- RFA for translational studies of variants identified through GEI-supported GWA studies ($2.4M/yr) in FY09-FY10

Challenges in ensuring participant and patient confidentiality, reducing the potential for discrimination and stigmatization, and dealing with the psychosocial impact of genetic findings will be addressed throughout the GEI Genetics Program, but will be a particular focus of the Clinical Translation Group.

EXPOSURE BIOLOGY PROGRAM

Rationale

The Exposure Biology Program will develop improved methods for precise measurement of environmental exposures, diet, physical activity, psychosocial stress, and addictive substances. In addition to the development of personalized sensors of environmental exposure, we will develop biological "fingerprints" that are indicative of activation of common pathogenic mechanisms such as oxidative stress, epigenetics, and DNA damage. These biomarkers of response will be coupled to the development of biosensors to enhance the utility of these biomarkers in predicting exposure to broad categories of toxins, dietary factors, physical activity, psychosocial stressors, and addictive substances. These more personalized measures of exposure and response are needed to critically evaluate the role of the environment in the development of genetic diseases.

Environmental Sensors

The Environmental Sensors initiatives will focus on improving the measurement of environmental chemical and biological agents, diet, physical activity, psychosocial stressors, and addictive substances specifically at the point of contact with the body. A total investment of $40M ($10M/year for FY07-FY10) will support new initiatives, including:

- RFA on new technologies for measuring dietary intake and physical activity using hand-held sensors, scanners or other devices, personal digital assistants (PDAs), imaging detection software, or wireless technology, and new technologies for measuring motion simultaneously with physiologic indicators of response (heart rate, respiration) with temporal and spatial resolution (up to $4M/yr for FY07-FY10).
- RFA on new technologies for measuring human contact exposure to priority environmental chemical/biological agents (e.g., airborne particulates, reactive gases, microbial toxins, solvents, pesticides, and mold/microbial toxins) with temporal and spatial resolution (up to $4M/yr for FY07-FY10).
- RFA on new technologies for measuring exposure to psychosocial stress and addictive substance usage including the use of hand-held devices for automated self-report and recall, innovative software, wireless technology, or other technology (up to $2M/yr for FY07-FY10).
- Workshop on assessment of physiologic measures of psychosocial stressors ($100K) in FY07.

Biological Response Indicators

The Biological Response initiatives will focus on developing novel biomarkers that reflect common physiologic and pathogenic processes in human disease, represent critical homeostatic mechanisms, and are affected by both environmental and genetic factors. Focusing on the common biological pathways that are affected by genetic factors and a variety of environmental chemical and biological agents, diet, physical activity, psychosocial stress, and addictive substances will ensure that the assays and biomarkers that are developed through the program have relevant application across the NIH Institutes. The assays will generate panels of organ specific biological response indicators, reflecting changes in genes (epigenetics, DNA adducts, DNA damage), gene transcripts (transciptomics), proteins (proteomics), and metabolites (metabolomics), and other physiologic and clinical parameters in biological samples (blood, urine, tissue, buccal cells) from multiple model systems, from animal to human. In addition, field deployable biosensors will be developed taking advantage of developments in emerging fields, such as nanotechnology, molecular imaging, and microfluidics. The assays will be applied to specific biosamples to generate panels of response indicators reflecting components of key physiologic and pathogenic processes, such as oxidative stress, immune response and inflammation, epigenetics, DNA damage and apoptosis, endocrine disruption, and defects in drug metabolizing enzymes.

A total of $38M will be allocated for these initiatives ($8.5M/yr for FY07-FY10). In FY07-FY10, new initiatives will include:

- RFA on development of biological response indicators reflecting components of key physiologic and pathogenic processes, such as oxidative stress, immune response and inflammation, epigenetics, DNA damage and apoptosis, endocrine disruption, and defects in drug metabolizing enzymes (up to $4M/yr for FY07-FY10).
- RFA on development of Centers that integrate biological response indicators with the development of field deployable biosensors (up to $4.5M/yr for FY07-FY10).

The initial project supported under the Biological Response initiatives will be the Environmental Airway Disease Project, a two-year project beginning in FY06 ($4M). The Project will focus on developing assays and panels of biological response indicators for inflammation and oxidative stress from exposure to common airway toxins (lipopolysaccharide, ozone, cigarette smoke, and house dust mite allergen) in experimental murine models with differential susceptibility, and in parallel non-human primate and human systems.

Program Integration

The Genetics and Exposure Biology Programs of GEI will be integrated both scientifically and functionally. The Exposure Biology Program will develop novel exposure assessment technologies that can be applied in a timely manner to the GWA studies funded through the Genetics Program to better understand the role of gene-environment interaction in disease. Priority will be given to developing novel assays and biomarkers for exposures with presumed proximity to genetic effects within metabolic pathways. In FY09 and FY10, we will allocate up to $2.95M/yr to support the application of new technology to these studies. For the Genetics Program, priority will be given to selecting studies for genotyping that have stored biospecimens, high-quality environmental exposure data, and strong evidence for an environmental influence as well as genetic influence on the trait.